Amendments to the Drawings:

Please substitute the attached twelve Replacement Sheets of drawings for the existing ten sheets of drawings in the application. The Replacement sheets are formal versions of the drawings filed with the application. Thus, annotated versions of the original drawings are not included.

Attachment: Replacement Sheets

REMARKS

With entry of the instant amendment, claims 50-55 have been added. Thus, claims 1-4, 7-11, 13, 14, 16, 17, 22-26, 29-32, and 50-55 are pending in the application.

Applicants thank the Examiner for discussing the obviouness rejection and evidence provided by Applicants in the interview on March 1, 2005.

The new claims add no new matter. Support can be found throughout the application as filed.

Claim 50 recites a recombinant RFB4 disulfide-stabilized Fv (dsFv) antibody having a variable heavy chain (V_H) with a cysteine at amino acid position 44, which heavy chain is at least 95% identical to SEQ ID NO:2; and a variable light chain (V_L) with a cysteine at amino acid position 100, which light chain is at least 95% identical to SEQ ID NO:4. Support can be found, *e.g.*, at page 18, lines 24-29.

Claim 50 recites a prototype RFB4 dsFv. Support for the amendment can be found, *e.g.*, at page 18, lines 12-29, which describes various Fv fragments, including RFB4dsFv fragments, and further, refers to prototype sequences, SEQ ID NO:2 and SEQ ID NO:4.

We note that with regard to claim 50, it is the RFB4dsFV antibody moiety of the immunoconjugates that has V_H and V_L regions with the specified identity to SEQ NO:2 or NO:4 and the specified binding affinity.

Applicants also respectfully note that with regard to the recitation of "that binds to the same epitope as the prototype RFB4 antibody", the V_H and V_L regions of RFB4 antibody have been sequences. Thus, it is possible to retain the same binding specificity without actually having exact knowledge of the epitope, because the CDRs of the RFB4 V_H and V_L regions can readily be determined and maintained in the antibodies encompassed by claim 50. For example, page 19, lines 27-33 teach that residues positions and the VH and VL structures are identified using known methodology.

Rejection under 35 U.S.C. § 103

Claims 1-4, 7-11, 13, 14, 16, 17, 22-26, and 29-32 stand rejected as allegedly obvious over the cited art. Applicants respectfully traverse for reasons of record. Briefly, the Federal Circuit has held that a nucleic acid sequence is not obvious over general methods of isolating cDNA or DNA molecules *See, e.g., In re Deuel*, 34 USPQ2d, 1210. In *Deuel*, the Court stated that "no particular one of these DNA can be obvious unless there is something in the prior art to lead to the particular DNA" (emphasis added).

The references cited by the Examiner (Orlandi *et al*, Cabilly *et al.*, Boss *et al.*, and Hutson *et al.*) teach only general PCR methods of obtaining sequences of V_H and V_L genes. They do not teach that any particular sequences would be obtained. Further, Shen *et al,* cited as teaching a hybridoma that produced RFB4, teaches only that an RFB4 cell line was raised as described by Campana *et al.* (1985). This hybridoma was not deposited. There is nothing that suggests that this hybridoma would produce an "RFB4" antibody with the precise sequence set forth in SEQ ID NO:1.

Further, Applicants submitted a Declaration under 37 C.F.R. § 1.132 by David J. FitzGerald, which was mailed for filing on March 11, 2004.

As previously explained, in the Declaration, Dr. FitzGerald provides evidence that one of skill could not reasonably predict the high level of expression, retention of parental IgG binding affinity, and superior toxicity and efficacy of RFB4ds(Fv) immunoconjugates. He indicates that RFB4 expresses surprisingly well from the perspective of one of skill in the art. He first compares its expression property to that of another anti-CD22 antibody, an LL2. Next, he explains that the superior expression and binding characteristics are unpredictable, because the art cannot predict which antibody sequences will express well or be stable.

As explained in Applicants' response dated July 14, 2003, Krietman and Pastan (*Seminars in Cancer Biology* 6:297, 306, 1995, submitted with the response) teach on page 303 that sc and dsFV versions of LL2 immuntoxins had very low activity. The FitzGerald Declaration explains that they first attempted to express LL2 (an scFv, expressed as a recombinant fusion protein with PE38), but the immunotoxin did not express well. He notes that attempts to express a recombinant ds(fv)LL2 immuntoxin also failed due to the poor expression

characteristics of the individual variable claims. Thus, this comparison is valid, in that it compares antibodies to the same antigen, in the same expression format as the exemplary recombinant RFB4 immunotoxin conjugate described in the Examples of the instant application.

Further, Dr. FitzGerald attests to the fact that the finding that RFB4 immunotoxins retain the binding specificity and affinity of the parent RFB4 IgG is unusual. It is surprising, not only in contrast to LL2-containing immunoconjugates, but also in comparison to many recombinant immunotoxins.

Last, he reiterates that RFB4dsFv immunotoxins have over 100 times better than any immunotoxin that could be produced using LL2 as the binding moiety, and have potent antitumor activity in animals and in human phase I trials.

In summary, Dr. FitzGerald's Declaration under 37 C.F.R. provides evidence that one of skill in the art considers the superior expression, binding, and toxicity of RFB4dsFv to be surprising and unexpected.

As explained above, Applicants believe that the claims are patentable over the art. Applicants therefore respectfully request withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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Attachments
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